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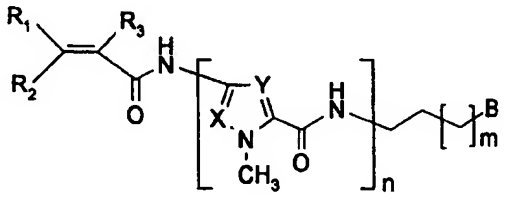
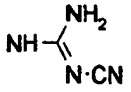
(54) Title: ACRYLOYL PEPTIDIC DERIVATIVES, PROCESS FOR THEIR PREPARATION AND THEIR USE AS ANTITUMOR AGENTS



(I)



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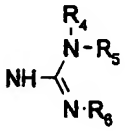

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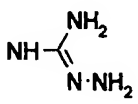

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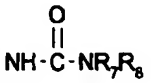

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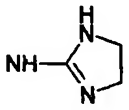

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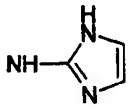

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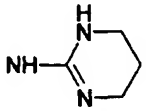

(7)

(57) Abstract: Compounds which are acryloyl peptidic derivatives of formula (I), wherein n is 3 or 4; m is 0, 1 or 2; X and Y are the same or different and are selected, independently for each heterocyclic ring, from N or CH; R_1 and R_2, the same or different, are selected from hydrogen, halogen or C_1-C_4 alkyl; R_3 is hydrogen or halogen, B is selected from the groups consisting of formulae (1), (2), (3), (4), (5), (6) and (7) wherein R_4, R_5, R_7, and R_8 are, independently from each other, hydrogen or C_1-C_4 alkyl; R_6 is hydrogen, hydroxy or C_1-C_4 alkyl; or a pharmaceutically acceptable salt thereof; with the provisos that X and Y are not both N atoms for the same heterocyclic ring; when all of X and Y are CH groups and m is 0, then at least one of R_4, R_5, or R_6 is other than hydrogen; when at least one of X and Y is other than CH, then at least one of R_4 and R_5 is other than hydrogen; are useful as antitumor agents.

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ACRYLOYL PEPTIDIC DERIVATIVES, PROCESS FOR THEIR PREPARATION AND THEIR USE AS ANTITUMOR AGENTS.

The present invention relates to new acryloyl peptidic compounds, to a process for their preparation, to pharmaceutical compositions containing them and to their use in therapy, in particular as antitumor agents.

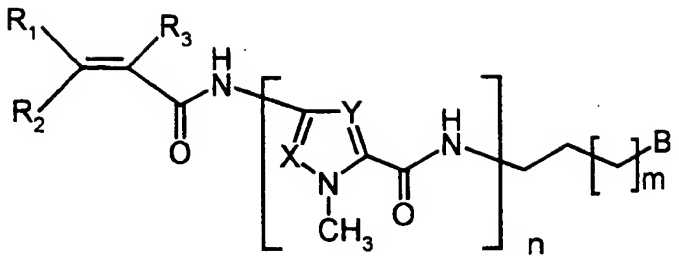
Peptidic derivatives, for instance Distamycin A and analogous thereof, are known in the art as antitumor agents.
Distamycin A is an antibiotic substance with antiviral and oncolytic properties, having a polypyrrole framework (Nature 203, 1064 (1964); J. Med. Chem. 32, 774-778 (1989)).

The international patent application WO 97/43258, in the name of the applicant, discloses acryloyl distamycin derivatives wherein the amidino moiety is replaced by nitrogen-containing ending groups such as, for instance, cyanamidino, N-methylamidino, ethylguanidino, amido, amidoximo, nitrile and the like.

Distamycin derivatives wherein at least one pyrrole ring of the aforementioned polypyrrole framework is replaced by an imidazole or pyrazole ring are also reported in the literature.
See, for a general reference, Anti-Cancer Drug Design 8, 173-192 (1993); J. Am. Chem. Soc. Vol. 114, 5911-5919 (1992); Anti-Cancer Drug Design 6, 501-517 (1991); patent applications EP-A-0246868 and WO 96/05196, both in the name of the applicant.

It has now been found that a new class of acryloyl peptidic derivatives, as defined hereinunder, is endowed with valuable biological properties.

Therefore, the present invention provides compounds which are acryloyl peptidic derivatives of formula



(I)

wherein:

n is 3 or 4;

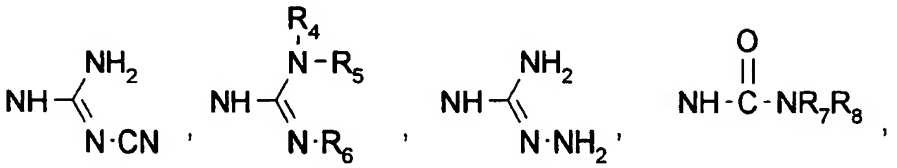
m is 0, 1 or 2;

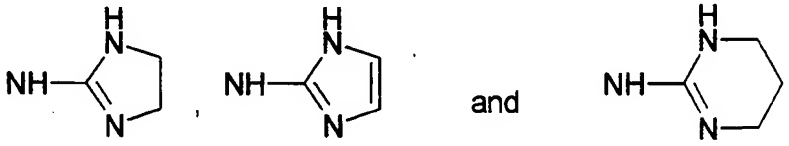
X and Y are the same or different and are selected, independently for each heterocyclic ring, from N or CH;

R_1 and R_2, the same or different, are selected from hydrogen, halogen or C_1-C_4 alkyl;

R_3 is hydrogen or halogen;

B is selected from the groups consisting of:





wherein R_4, R_5, R_7 and R_8 are, independently from each other, hydrogen or C_1-C_4 alkyl; R_6 is hydrogen, hydroxy or C_1-C_4 alkyl; or a pharmaceutically acceptable salt thereof;

provided that:

i) X and Y are not both N atoms for the same heterocyclic ring;

ii) when all of X and Y are CH groups and m is 0, then at least one of R_4, R_5 or R_6 is other than hydrogen;

iii) when at least one of X and Y is other than CH, then at least one of R_4 and R_5 is other than hydrogen.

The present invention includes within its scope also all the possible isomers covered by the compounds of formula

(I), both separately and in admixture, as well as the metabolites and the pharmaceutically acceptable bio-precursors (otherwise known as pro-drugs) of the compounds of formula (I).

In the present description, unless otherwise specified, the term alkyl includes straight or branched C_1-C_4 alkyl groups such as, for instance, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl, methyl and ethyl being preferred; the term halogen includes fluorine, chlorine, bromine and iodine, fluorine, chlorine or bromine being preferred.

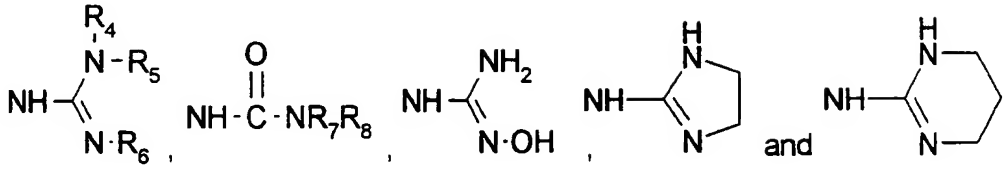
As above reported, X and Y are selected, independently for each heterocyclic ring of the polyheterocyclic chain, between N and CH. This means that within the compounds of formula (I) and for different heterocyclic rings, X can be either N as well as CH; the same applies to Y provided that X and Y are not contemporaneously N for a single heterocycle.
Examples for the said heterocycles are pyrrole, pyrazole and imidazole.

Pharmaceutically acceptable salts of the compounds of formula (I) are those with pharmaceutically acceptable inorganic or organic acids such as, for instance, hydrochloric, hydrobromic, sulphuric, nitric, acetic, propionic, succinic, malonic, citric, tartaric, methanesulfonic and p-toluenesulfonic acid.

A preferred class of compounds, according to the present invention, is represented by the above formula (I) wherein R_4, R_5, R_7 and R_8 are, independently from each other, hydrogen, methyl or ethyl and R_6 is hydrogen, hydroxy, methyl or ethyl.

Even more preferred, within this class, are the compounds

of formula (I) wherein
n is 3 or 4;
m is 0, 1 or 2;
X and Y are CH;
R_1 and R_2 are hydrogen;
R_3 is chlorine or bromine;
B is selected from



wherein R_4, R_5, R_7 and R_8 are, independently from each other, hydrogen or methyl and R_6 is hydrogen, hydroxy or methyl; provided that when m is 0, at least one of R_4, R_5 or R_6 is other than hydrogen.

Examples of specific compounds according to the present invention, especially in the form of salts, preferably with hydrochloric acid, are the following:

(1) N-(5-{[(5-{[(5-{[(2-{[amino(methylimino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide

(2) N-(5-{[(5-{[(5-{[(2-{[amino(methylimino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-chloroacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide

(3) 4-[(2-bromoacryloyl)amino]-N-(5-{[(5-{[(5-{[(2-{[imino(methylamino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-1-methyl-1H-pyrrole-2-carboxamide

(4) 4-[(2-chloroacryloyl)amino]-N-(5-{[(5-{[(5-{[(2-

{[imino(methylamino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-1-methyl-1H-pyrrole-2-carboxamide

(5) 4-[(2-bromoacryloyl)amino]-N-(5-{[(5-{[(5-{[(2-{[(dimethylamino)(imino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-1-methyl-1H-pyrrole-2-carboxamide

(6) 4-[(2-chloroacryloyl)amino]-N-(5-{[(5-{[(5-{[(2-{[(dimethylamino)(imino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-1-methyl-1H-pyrrole-2-carboxamide

(7) 4-[(2-bromoacryloyl)amino]-1-methyl-N-(1-methyl-5-{[(1-methyl-5-{[(1-methyl-5-{[(2-{[(methylamino)(methylimino)methyl]amino}ethyl)amino]carbonyl}-1H-pyrrol-3-yl)amino]carbonyl}-1H-pyrrol-3-yl)amino]carbonyl}-1H-pyrrol-3-yl)-1H-pyrrole-2-carboxamide

(8) 4-[(2-chloroacryloyl)amino]-1-methyl-N-(1-methyl-5-{[(1-methyl-5-{[(1-methyl-5-{[(2-{[(methylamino)(methylimino)methyl]amino}ethyl)amino]carbonyl}-1H-pyrrol-3-yl)amino]carbonyl}-1H-pyrrol-3-yl)amino]carbonyl}-1H-pyrrol-3-yl)-1H-pyrrole-2-carboxamide

(9) N-{5-[({5-[({5-[({2-[(aminocarbonyl)amino]ethyl}amino)carbonyl]-1-methyl-1H-pyrrol-3-yl}amino)carbonyl]-1-methyl-1H-pyrrol-3-yl}amino)carbonyl]-1-methyl-1H-pyrrol-3-yl}-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide

(10) N-{5-[({5-[({5-[({2-[(aminocarbonyl)amino]ethyl}amino)carbonyl]-1-methyl-1H-pyrrol-3-yl}amino)carbonyl]-1-methyl-1H-pyrrol-3-yl}amino)carbonyl]-1-methyl-1H-pyrrol-3-yl}-4-[(2-chloroacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide

(11) 4-[(2-bromoacryloyl)amino]-1-methyl-N-(1-methyl-5-{[(1-methyl-5-{[(1-methyl-5-{[(2-

{[(methylamino)carbonyl]amino}ethyl)amino]carbonyl}-1H-pyrrol-3-yl)amino]carbonyl}-1H-pyrrol-3-yl)amino]carbonyl}-1H-pyrrol-3-yl)-1H-pyrrole-2-carboxamide

(12) 4-[(2-chloroacryloyl)amino]-1-methyl-N-(1-methyl-5-{[(1-methyl-5-{[(1-methyl-5-{[(2-{[(methylamino)carbonyl]amino}ethyl)amino]carbonyl}-1H-pyrrol-3-yl)amino]carbonyl}-1H-pyrrol-3-yl)amino]carbonyl}-1H-pyrrol-3-yl)-1H-pyrrole-2-carboxamide

(13) N-(5-{[(5-{[(5-{[(2-{[amino(hydroxyimino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide

(14) N-(5-{[(5-{[(5-{[(2-{[amino(hydroxyimino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-chloroacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide

(15) 4-[(2-bromoacryloyl)amino]-N-[5-({[5-({[5-({[2-(4,5-dihydro-1H-imidazol-2-ylamino)ethyl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]-1-methyl-1H-pyrrole-2-carboxamide

(16) 4-[(2-chloroacryloyl)amino]-N-[5-({[5-({[5-({[2-(4,5-dihydro-1H-imidazol-2-ylamino)ethyl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]-1-methyl-1H-pyrrole-2-carboxamide

(17) 4-[(2-bromoacryloyl)amino]-N-[5-({[5-({[5-({[2-(1H-imidazol-2-ylamino)ethyl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]-1-methyl-1H-pyrrole-2-carboxamide

(18) 4-[(2-chlorooacryloyl)amino]-N-[5-({[5-({[5-({[2-(1H-

imidazol-2-ylamino)ethyl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]-1-methyl-1H-pyrrole-2-carboxamide

(19) 4-[(2-bromoacryloyl)amino]-1-methyl-N-[1-methyl-5-({[1-methyl-5-({[1-methyl-5-({[2-(1,4,5,6-tetrahydro-2-pyrimidinylamino)ethyl]amino}carbonyl)-1H-pyrrol-3-yl]amino}carbonyl)-1H-pyrrol-3-yl]amino}carbonyl)-1H-pyrrol-3-yl]-1H-pyrrole-2-carboxamide

(20) 4-[(2-chloroacryloyl)amino]-1-methyl-N-[1-methyl-5-({[1-methyl-5-({[1-methyl-5-({[2-(1,4,5,6-tetrahydro-2-pyrimidinylamino)ethyl]amino}carbonyl)-1H-pyrrol-3-yl]amino}carbonyl)-1H-pyrrol-3-yl]amino}carbonyl)-1H-pyrrol-3-yl]-1H-pyrrole-2-carboxamide

(21) N-(5-{[(5-{[(5-{[(2{[amino(imino)methyl]amino}propyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide

(22) N-(5-{[(5-{[(5-{[(2{[amino(imino)methyl]amino}propyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-chloroacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide

(23) 4-[(2-bromoacryloyl)amino]-1-methyl-N-(1-methyl-5-{[(1-methyl-5-{[(1-methyl-5-{[(2-{[(methylamino)(methylimino)methyl]amino}propyl)amino]carbonyl}-1H-pyrrol-3-yl)amino]carbonyl}-1H-pyrrol-3-yl)amino]carbonyl}-1H-pyrrol-3-yl)-1H-pyrrole-2-carboxamide

(24) 4-[(2-chloroacryloyl)amino]-1-methyl-N-(1-methyl-5-{[(1-methyl-5-{[(1-methyl-5-{[(2-{[(methylamino)(methylimino)methyl]amino}propyl)amino]carbonyl}-1H-pyrrol-3-yl)amino]carbonyl}-1H-pyrrol-3-yl)amino]carbonyl}-1H-pyrrol-3-yl)-1H-pyrrole-2-carboxamide

(25) N-{5-[({5-[({5-[({2-[(aminocarbonyl)amino]ethyl}amino)carbonyl]-1-methyl-1H-pyrrol-3-

yl}amino)carbonyl]-1-methyl-1H-pyrrol-3-yl}amino)carbonyl]-1-methyl-1H-pyrrol-3-yl}-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide

(26) N-{5-[({5-[({5-[({2-[(aminocarbonyl)amino]ethyl}amino)carbonyl]-1-methyl-1H-pyrrol-3-yl}amino)carbonyl]-1-methyl-1H-pyrrol-3-yl}amino)carbonyl]-1-methyl-1H-pyrrol-3-yl}-4-[(2-chloroacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide

(27) 4-[(2-bromoacryloyl)amino]-N-[5-({[5-({[5-({[2-(4,5-dihydro-1H-imidazol-2-ylamino)propyl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]-1-methyl-1H-pyrrole-2-carboxamide

(28) 4-[(2-chloroacryloyl)amino]-N-[5-({[5-({[5-({[2-(4,5-dihydro-1H-imidazol-2-ylamino)propyl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]-1-methyl-1H-pyrrole-2-carboxamide

(29) 4-[(2-bromoacryloyl)amino]-1-methyl-N-[1-methyl-5-({[1-methyl-5-({[1-methyl-5-({[2-(1,4,5,6-tetrahydro-2-pyrimidinylamino)propyl]amino}carbonyl)-1H-pyrrol-3-yl]amino}carbonyl)-1H-pyrrol-3-yl]amino}carbonyl)-1H-pyrrol-3-yl]-1H-pyrrole-2-carboxamide

(30) 4-[(2-chloroacryloyl)amino]-1-methyl-N-[1-methyl-5-({[1-methyl-5-({[1-methyl-5-({[2-(1,4,5,6-tetrahydro-2-pyrimidinylamino)propyl]amino}carbonyl)-1H-pyrrol-3-yl]amino}carbonyl)-1H-pyrrol-3-yl]amino}carbonyl)-1H-pyrrol-3-yl]-1H-pyrrole-2-carboxamide

(31) N-(5-{[(5-{[(2-{[amino(methylimino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide

(32) 4-[(2-bromoacryloyl)amino]-1-methyl-N-(1-methyl-5-{[(1-methyl-5-{[(2-{[(methylamino)(methylimino)methyl]amino}ethyl)amino]carbonyl}-1H-pyrrol-3-yl)amino]carbonyl}-1H-pyrrol-3-yl)-1H-pyrrole-2-

carboxamide

(33) 4-[(2-bromoacryloyl)amino]-1-methyl-N-(1-methyl-5-{[(1-methyl-5-{[(2-[(aminocarbonyl)amino]ethyl)amino]carbonyl}-1H-pyrrol-3-yl)amino]carbonyl}-1H-pyrrol-3-yl)-1H-pyrrole-2-carboxamide

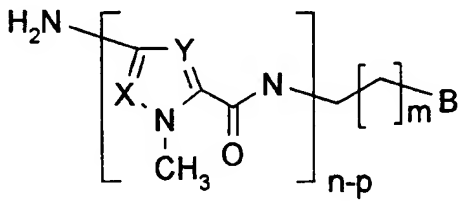
(34) 4-[(2-bromoacryloyl)amino]-N-[5-({[5-({[2-(4,5-dihydro-1H-imidazol-2-ylamino)ethyl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]-1-methyl-1H-pyrrole-2-carboxamide

(35) 4-[(2-bromoacryloyl)amino]-1-methyl-N-[1-methyl-5-({[1-methyl-5-({[1-methyl-5-({[2-(1,4,5,6-tetrahydro-2-pyrimidinylamino)ethyl]amino}carbonyl)-1H-pyrrol-3-yl]amino}carbonyl)-1H-pyrrol-3-yl]amino}carbonyl)-1H-pyrrol-3-yl]-1H-pyrrole-2-carboxamide

(36) N-(5-{[(5-{[(5-{[(2{[amino(imino)methyl]amino}butyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide

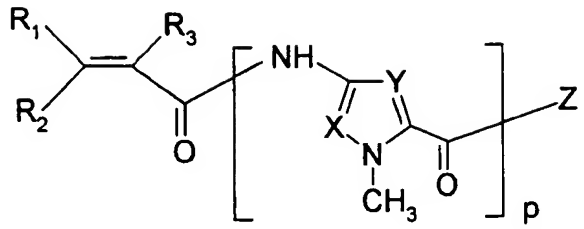
(37) N-(5-{[(5-{[(5-{[(2{[amino(imino)methyl]amino}butyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-chloroacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide.

According to a further object of the present invention, the compounds of formula (I) can be prepared by a process which comprises reacting a compound of formula



(II)

with a compound of formula



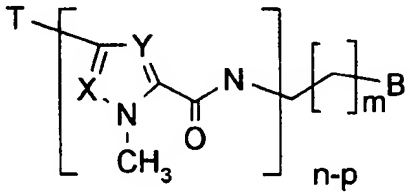
(III)

wherein n, m, X, Y, B, R_1, R_2, R_3, X and Y are as defined above; p is 0 or 1 and Z is hydroxy or a suitable leaving group; and, if desired,

converting a compound of formula (I) into a pharmaceutically acceptable salt thereof.

Within the above compounds of formula (III), Z is hydroxy or a suitable leaving group for instance selected from chlorine, 2,4,5-trichlorophenoxy, pivaloyl, and the like.

The compounds of formula (II) may be prepared by converting a compound of formula



(IV)

wherein X, Y, B, n, m and p are as defined above and T is nitro or an amino group properly protected according to conventional techniques.

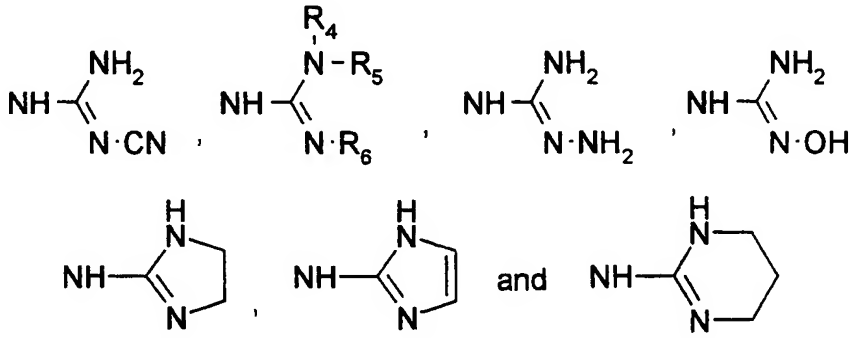
As an example, the conversion of a compound of formula (IV) wherein T is nitro into a compound of formula (II) may be carried out under hydrogen pressure in the presence of suitable hydrogenation catalysts, e.g. palladium on charcoal, into a suitable solvent such as dioxane, methanol, ethanol and mixtures thereof, at room temperature.

Likewise, the conversion of a compound of formula (IV) wherein T is a protected amino group into the free amino derivative of formula (II) may be carried out according to conventional deprotection techniques known in the art. See,

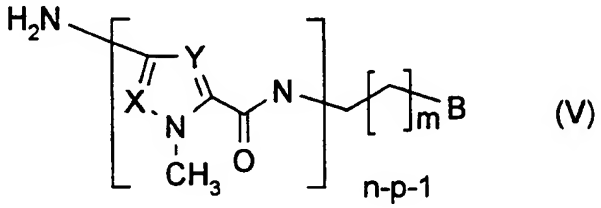
for a general reference, *J. Org. Chem.* 43, 2285, **1978**; *J. Chem. Soc. Chem. Commun.* 495, **1980**.

Examples of suitable amino protecting groups are, for instance, t-butyloxycarbonyl, triphenylmethyl or, more preferably, carbobenzyloxy and formyl.

In their tun, the compounds of formula (IV) wherein B is selected from

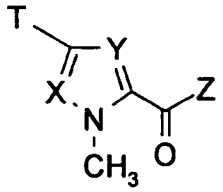


can be prepared by reacting a compound of formula (V)



(V)

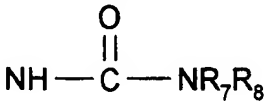
with a compound of formula (VI):



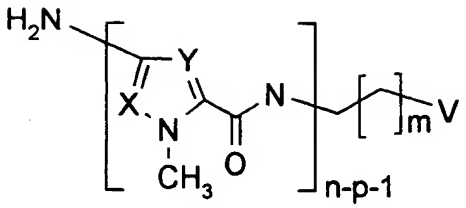
(VI)

wherein m, n, p, X, Y, T, B and Z are as defined above.

Instead, the compounds of formula (IV) wherein B is



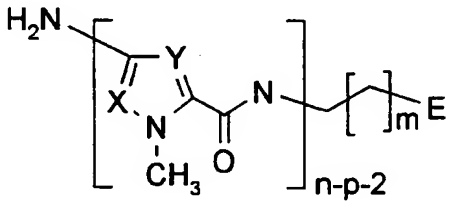
can be prepared by first reacting a compound of formula



(VII)

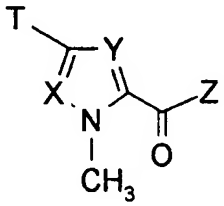
wherein X, Y, n, m and p are as defined above and V is a protected amino group, e.g. *t*-butoxycarbonyl-amino, with a compound of formula (VI), by subsequently removing the protecting group and by coupling the resultant compound with a suitable amine in presence of 1,1'-carbonyldiimidazole (CDI).

The compounds of formula (V) and (VII) can be prepared by reacting a compound of formula



(VIII)

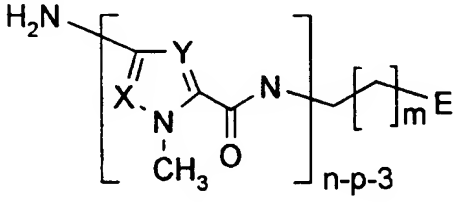
with a compound of formula



(VI)

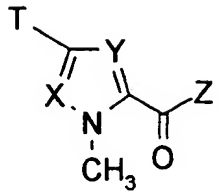
wherein m, n, p, X, Y, T and Z are as defined above and E is equal to B or V as defined within formulae (V) or (VII), respectively.

The compounds of formula (VIII) can be prepared by reacting a compound of formula



(IX)

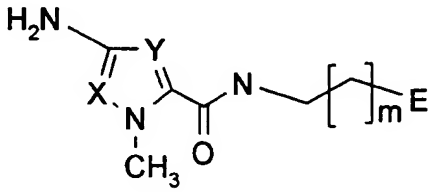
with a compound of formula



(VI)

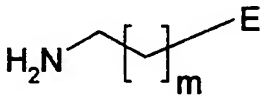
wherein m, n, p, X, Y, T, Z and E are as defined above.

The compounds of formula (VIII) wherein n=4 and p=1 or n=3 and p=0 and those of formula (IX) wherein n=4 and p=0, all of which represented as compounds of formula



(X)

can be obtained by reacting a compound of formula (VI) with a compound of formula (XI):



(XI)

wherein X, Y, m and E are as defined above.

From the foregoing, it is clear to the skilled man that the compounds of formula (VIII) wherein n=3 and p=1 and those of formula (IX) wherein n=3 and p=0, exactly correspond to the above compounds of formula (XI).

The reaction between a compound of formula (II) and a compound of formula (III) or between a compound of formula (V), (VII), (VIII), (IX) and (XI) with a compound of formula (VI), can all be carried out according to known methods, for instance as described in the aforementioned EP-A-246,868 and WO 96/05196.

The compounds of formula (VI) are known or can be easily prepared by known procedure as reported, for instance, in WO 96/05196; J.C.S. 1947-1032 and JACS 62, 3495 (1940).

The compounds of formula (XI) are known or can be easily

prepared by known procedure such as, for instance, *Synt. Comm.* 28, 741, **1998**; *Synt. Comm.* 20, 2559-2564, 3433-3437, **1990**; *J. Chem. Soc. Perkin Trans I*, 173, **1990**; *J. Chem. Soc.* 3127, **1963**; *J. Org. Chem.* 275, **1963**; *J. Het. Chem.* 2424, **1981**; *J. Org. Chem.* 1157, **1959**; *J. Chem. Soc.*, 1629, **1958**; *J. Chem. Soc.* 39, **1929**.

The compounds of formula (III) and (VI) are known or may be obtained by known methods (see, for a general reference, *Tetrahedron*, 34, 2389, **1978**; *J. Org. Chem.*, 46, 3492, **1981**; *J. Org. Chem.*, 52, 3493, **1987**; WO 96/05196 and WO 97/43258).

The optional conversion of a compound of formula (I) into a pharmaceutically acceptable salt, as well as the preparation of a free compound starting from a salt, may be carried out by known standard methods.
Well known procedures such as, e.g., fractional crystallization or chromatography may also be followed for separating a mixture of isomers of formula (I) into the single isomers.
The compounds of formula (I) may be purified by conventional techniques such as, e.g., silica gel or alumina column chromatography, and/or by recrystallization from an organic solvent such as, e.g., a lower aliphatic alcohol, e.g. methyl, ethyl or isopropyl alcohol, or dimethylformamide.

The compounds of the invention show cytotoxic properties towards tumor cells and are thus useful as antineoplastic agents, e.g. to inhibit the growth of various tumors such as, for instance, carcinomas, e.g. mammary carcinoma, lung carcinoma, bladder carcinoma, colon carcinoma, ovary and endometrial tumors. Other neoplasias in which the compounds of the invention could find application are, for instance, sarcomas, e.g. soft tissue and bone sarcomas, and the

hematological malignancies such as, e.g., leukemias.

The antitumor activity of the compounds of formula (I) was evaluated in vitro by cytotoxicity studies carried out on murine L1210 leukemia cell. Cells were derived from in vivo tumors and established in cell culture. Cells were used until the tenth passage. Cytotoxicity was determined by counting surviving cells after 4 hours treatment and 48 hours growth in drug-free medium.
The percentage of cell growth in the treated cultures was compared with that of controls. Doses inhibiting 50% of the cellular growth in respect to controls, expressed as ID_{50} values, were calculated on dose-response curves.

The compounds of the invention can be administered by the usual routes, for example, parenterally, e.g. by intravenous injection or infusion, intramuscularly, subcutaneously, topically or orally.
The dosage depends on the age, weight and conditions of the patient and on the administration route.
For example, a suitable dosage for administration to adult humans may range from about 0.05 to about 100 mg pro dose from 1 to 4 times a day.
The pharmaceutical compositions object of the present invention contain an effective amount of a compound of formula (I), as the active substance, in association with one or more pharmaceutically acceptable excipients.
The pharmaceutical compositions of the invention are usually prepared following conventional methods and are administered in a pharmaceutically suitable form.
For instance, solutions for intravenous injection or infusion may contain sterile water as a carrier or, preferably, they may be in the form of sterile aqueous isotonic saline solutions.
Suspensions or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil,

ethyl oleate, glycols, e.g. propylene glycol and, if desired, a suitable amount of lidocaine hydrochloride.

In the form for topical application, e.g. creams, lotions or pastes for use in dermatological treatment, the active ingredient may be mixed with conventional oleaginous or emulsifying excipients.

The solid oral forms, e.g. tablets and capsules, may contain, together with the active compound, diluents, e.g. lactose, dextrose, saccharose, cellulose, corn starch and potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents, e.g. starches, arabic gums, gelatin, methylcellulose, carboxymethyl-cellulose, polyvinylpyrrolidone; disaggregating agents, e.g. a starch, alginic acid, alginates, sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents, for instance, lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Said pharmaceutical preparations may be manufactured in a known manner, for example by means of mixing, granulating, tabletting, sugar-coating, or film-coating processes.

Furthermore, according to the present invention, there is provided a method of treating tumors in a patient in need of it which comprises administering to the said patient a composition of the invention.

The following examples are herewith intended to better illustrate the present invention without posing any limitation to it.

The abbreviations DMF, Et_2O, EtOH, DCM, CDI, EtOAc and DMSO-d_6 stand for dimethylformamide, diethyl ether, ethanol, methylene chloride, 1,1'carbonyldiimidazole, ethyl acetate and deutero-dimethylsulfoxide, respectively.

Example 1

The intermediate N-(4,5-dihydro-1H-imidazol-2-yl)-1,2-

ethanediamine dihydrochloride

To a solution of N-BOC ethylendiamine (1.6 g) in dry EtOH (20 ml), 2-methyltio-2-imidazoline hydroiodide (2.9 g), prepared as reported in *Synth. Comm.* 28, 741-746, **1998,** was added. The reaction mixture was refluxed for 8 h, the solvent evaporated under vacuum and the crude derivative dissolved in a solution of 5N HCl/MeOH (30 ml). The reaction solution was stirred at room temperature for 3 h, the solvent evaporated under vacuum and the crude product washed with cool EtOH (15 ml) and then with Et_2O (10 ml), yielding the pure intermediate (1.2 g; y=80%) as a yellow powder.

m.p.(Et2O) 135-138 °C

PMR (DMSO-d_6) δ: 8.30 (bs, 3H), 8.22 (t, J=5.8 Hz, 1H), 3.87 (m, 4H), 3.36 (m, 4H).

By analogous procedure and by using the opportune starting materials the following compounds can be obtained:

N-(4,5-dihydro-1H-imidazol-2-yl)-1,3-propanediamine dihydrochloride;

N-(1H-imidazol-2-yl)-1,2-ethanediamine dihydrochloride;

N-(1H-imidazol-2-yl)-1,2-propanediamine dihydrochloride;

N-(2-aminoethyl)-N-(1,4,5,6-tetrahydropyrimidin-2-yl)amine dihydrochloride;

N-(3-aminopropyl)-N-(1,4,5,6-tetrahydropyrimidin-2-yl)amine dihydrochloride;

The intermediate

{[(methylamino)(methylimino)methyl]sulfanyl}methane

To a solution of dimethylthiourea (4.17g) in dry EtOH (20 ml), iodomethane (2.8 ml) was added. The reaction was refluxed for 3 h, the solvent evaporated under vacuum, and the crude compound purified by precipitation EtOH/Et_2O thus yielding the pure intermediate (9.8 g; y=98%) as a yellow powder.

The intermediate

N-(2-aminoethyl)-N',N''-dimethylguanidine hydrochloride

To a solution of N-BOC ethylendiamine (1.6 g) in dry EtOH (20

ml) {[(methylamino)(methylimino)methyl]sulfanyl}methane (3 g) was added. The reaction was refluxed for 8 h, the solvent evaporated under vacuum and the yellow crude oil dissolved in a solution of saturated hydrochloric acid in methanol. The reaction solution was stirred at room temperature for 3 h, the solvent evaporated under vacuum yielding the crude intermediate as a yellow oil (1.2 g; y = 60%)

PMR (DMSO-d_6) δ: 8.18 (bs, 1H), 7.40 (bs, 1H), 3.40-3.20 (m, 4H), 2.81 (m, 6H).

By analogous procedure and by using the opportune starting materials the following compounds can be obtained:

N-(2-aminoethyl)-N'-methylguanidine hydrochloride;

N-(3-aminopropyl)-N'-methylguanidine hydrochloride;

N-(2-aminoethyl)-N''-methylguanidine hydrochloride;

N-(3-aminopropyl)-N''-methylguanidine hydrochloride;

N'-(2-aminoethyl)-N,N-dimethylguanidine hydrochloride;

N'-(3-aminopropyl)-N,N-dimethylguanidine hydrochloride;

The intermediate

N-(3-aminopropyl)guanidine dihydrochloride

To a solution of N-BOC-propylendiamine (1.5 g) in dry EtOH (25 ml), 2-methyl-2-thiopseudourea iodoidride (2.24 g) was added. The reaction was refluxed for 3 h, the solvent evaporated under vacuum, and the crude yellow oil dissolved in a solution of 5N HCl/MeOH (30 ml). The reaction solution was stirred at room temperature for 3 h, the solvent evaporated under vacuum and the residue was then treated with EtOH (15 ml) and with Et_2O (10 ml). The obtained emulsion was cooled and the solvent evaporated. The solid obtained after cooling of the yellow oil was washed with Et_2O yielding the intermediate as a white solid (1.15 g; y=70%).

PMR (DMSO-d_6) δ: 8.24 (m, 6H), 3.42 (m, 2H), 2.86 (m, 2H), 1.91 (m, 2H).

By analogous procedure and by using the opportune starting material the following compound can be obtained:

N-(4-aminobutyl)guanidine dihydrochloride

Example 2

4-[(2-bromoacryloyl)amino]-N-[5-({[5-({[5-({[2-(4,5-dihydro-1H-imidazol-2-ylamino)ethyl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride **(comp.15)**

Step I: The intermediate N-[2-(4,5-dihydro-1H-imidazol-2-ylamino)ethyl]-1-methyl-4-nitro-1H-pyrrole-2-carboxamide hydrochloride

To a solution of N-(4,5-dihydro-1H-imidazol-2-yl)-1,2-ethanediamine dihydrochloride(1.2 g), $NaHCO_3$ (1.5 g) in a mixture water/dioxane 1/1 (30 ml) a solution of 1-methyl-4-nitro-1H-pyrrole-2-carbonyl chloride, [prepared as reported in WO 96/05196] (2 g) in dry dioxane(5 ml) was added dropwise at room temperature. The reaction was stirred for 1h, the solvent evaporated under vacuum and the crude residue purified by flash chromatography (methylene chloride/methanol:8/2) giving the intermediate (1.1 g, y= 60%) as a yellow powder.

m.p. 168-170 °C

PMR (DMSO-d_6) δ: 8.46 (m,1H), 8.37 (t, J=5.8 Hz, 1H), 8.14 (d, J=1.7 Hz, 1H), 7.54 (d, J=1.7 Hz, 1H), 3.91 (s, 3H), 3.55 (m, 4H), 3.50 (m, 2H), 3.35 (m, 2H).

By analogous procedure and by using the opportune starting materials the following compounds can be obtained:

N-[2-(4,5-dihydro-1H-imidazol-2-ylamino)propyl]-1-methyl-4-nitro-1H-pyrrole-2-carboxamide hydrochloride;

N-(2-{[amino(imino)methyl]amino}propyl)-1-methyl-4-nitro-1H-pyrrole-2-carboxamide hydrochloride

m.p. 156-158 °C

PMR (DMSO-d_6) δ: 8.54 (t, J=7.2 Hz, 1H), 8.13 (m, 1H), 7.83 (m, 1H), 7.49 (m, 1H), 7.29 (bs, 4H), 3.91 (s, 3H), 3.38 (m, 2H), 3.25 (m, 2H), 1.74 (m, 2H);

N-(2-{[amino(imino)methyl]amino}butyl)-1-methyl-4-nitro-1H-pyrrole-2-carboxamide hydrochloride;

N-[5-({[2-(4,5-dihydro-1H-imidazol-2-ylamino)ethyl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]-1-methyl-4-nitro-1H-pyrrole-2-carboxamide hydrochloride
m.p. 211-214 °C
PMR (DMSO-d_6) δ: 10.36 (s, 1H), 8.49 (m, 2H), 8.41 (t, J=5.8 Hz, 1H), 8.23 (t, J=5.8 Hz, 1H), 8.17 (d, J=1.7 Hz, 1H), 7.63 (d, J=1.7 Hz, 1H), 7.24 (d, J=1.7 Hz, 1H), 6.94 (d, J=1.7 Hz, 1H), 4.14 (m, 2H), 3.95 (s, 3H), 3.81 (s, 3H), 3.58 (m, 2H), 3.60 (m, 4H);
N-[5-({[2-(4,5-dihydro-1H-imidazol-2-ylamino)propyl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]-1-methyl-4-nitro-1H-pyrrole-2-carboxamide hydrochloride;
N-(2-{[amino(imino)methyl]amino}ethyl)-1-methyl-4-{[(1-methyl-4-nitro-1H-pyrrol-2-yl)carbonyl]amino}-1H-pyrrole-2-carboxamide hydrochloride
m.p. 275-277 °C
PMR (DMSO-d_6) δ: 10.30 (s, 1H), 8.21 (t, J=5.8 Hz, 1H), 8.19 (s, 1H), 7.69 (t, J=5.8 Hz, 1H), 7.60 (d, J=1.7 Hz, 1H), 7.22 (d, J=1.7 Hz, 1H), 7.21 (bs, 4H), 6.90 (d, J=1.7 Hz, 1H), 3.95 (s, 3H), 3.81 (s, 3H), 3.16 (m, 4H), 1.69 (m, 2H);
N-[5-({[2-(4,5-dihydro-1H-imidazol-2-ylamino)ethyl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]-1-methyl-4-{[(1-methyl-4-nitro-1H-pyrrol-2-yl)carbonyl]amino}-1H-pyrrole-2-carboxamide hydrochloride
m.p. 251-255 °C
PMR (DMSO-d_6) δ: 10.38 (s, 1H), 10.02 (s, 1H), 8.37 (m, 2H), 8.33 (t, J=5.8 Hz, 1H), 8.20 (t, J=5.8 Hz, 1H), 8.17 (d, J=1.7 Hz, 1H), 7.65 (d, J=1.7 Hz, 1H), 7.28 (d, J=1.7 Hz, 1H), 7.21 (d, J=1.7 Hz, 1H), 7.06 (d, J=1.7 Hz, 1H), 6.94 (d, J=1.7 Hz, 1H), 3.97 (m, 2H), 3.95 (s, 3H), 3.91 (s, 3H), 3.85 (s, 3H), 3.58 (m, 2H), 3.57 (m, 4H);
N-[5-({[2-(4,5-dihydro-1H-imidazol-2-ylamino)propyl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]-1-methyl-4-{[(1-methyl-4-nitro-1H-pyrrol-2-yl)carbonyl]amino}-1H-pyrrole-2-carboxamide hydrochloride;

N-(5-{[(2-{[amino(imino)methyl]amino}propyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-1-methyl-4-{[(1-methyl-4-nitro-1H-pyrrol-2-yl)carbonyl]amino}-1H-pyrrole-2-carboxamide hydrochloride

m.p. 278-281 °C

PMR (DMSO-d_6) δ: 10.12 (s, 1H), 9.99 (s, 1H), 8.21 (t, J=5.8 Hz, 1H), 8.19 (s, 1H), 7.69 (t, J=5.8 Hz, 1H), 7.60 (d, J=1.7 Hz, 1H), 7.22 (d, J=1.7 Hz, 1H), 7.21 (bs, 4H), 7.07 (m, 2H), 6.98 (d, J=1.7 Hz, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 3.81 (s, 3H), 3.16 (m, 4H), 1.71 (m, 2H);

N-(5-{[(2-{[amino(imino)methyl]amino}butyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-1-methyl-4-{[(1-methyl-4-nitro-1H-pyrrol-2-yl)carbonyl]amino}-1H-pyrrole-2-carboxamide hydrochloride;

N-(2-{[amino(methylimino)methyl]amino}ethyl)-1-methyl-4-nitro-1H-pyrrole-2-carboxamide hydrochloride;

N-(5-{[(2-{[amino(methylimino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-1-methyl-4-nitro-1H-pyrrole-2-carboxamide hydrochloride;

N-(5-{[(2-{[amino(methylimino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-1-methyl-4-{[(1-methyl-4-nitro-1H-pyrrol-2-yl)carbonyl]amino}-1H-pyrrole-2-carboxamide hydrochloride;

N-(2-{[imino(methylamino)methyl]amino}ethyl)-1-methyl-4-nitro-1H-pyrrole-2-carboxamide hydrochloride;

N-(5-{[(2-{[imino(methylamino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-1-methyl-4-nitro-1H-pyrrole-2-carboxamide hydrochloride;

N-(5-{[(2-{[imino(methylamino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-1-methyl-4-{[(1-methyl-4-nitro-1H-pyrrol-2-yl)carbonyl]amino}-1H-pyrrole-2-carboxamide hydrochloride;

N-(2-{[(dimethylamino)(imino)methyl]amino}ethyl)-1-methyl-4-nitro-1H-pyrrole-2-carboxamide hydrochloride;

N-(5-{[(2-{[(dimethylamino)(imino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-1-methyl-4-nitro-1H-pyrrole-2-carboxamide hydrochloride;

N-(5-{[(2-{[(dimethylamino)(imino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-1-methyl-4-{[(1-methyl-4-nitro-1H-pyrrol-2-yl)carbonyl]amino}-1H-pyrrole-2-carboxamide hydrochloride;

1-methyl-N-(2-{[(methylamino)(methylimino)methyl]amino}ethyl)-4-nitro-1H-pyrrole-2-carboxamide hydrochloride

m.p. 130-132 °C

PMR (DMSO-d_6) δ: 8.87 (t, J=5.8 Hz, 1H), 8.16 (s, 1H), 7.72 (m, 2H), 7.56 (m, 1H), 7.53 (d, J=1.7 Hz, 1H), 3.91 (s, 3H), 3.39 (m, 4H), 2.73 (m, 6H);

1-methyl-N-(2-{[(methylamino)(methylimino)methyl]amino}propyl)-4-nitro-1H-pyrrole-2-carboxamide hydrochloride;

1-methyl-N-(1-methyl-5-{[(2-{[(methylamino)(methylimino)methyl]amino}ethyl)amino]carbonyl}-1H-pyrrol-3-yl)-4-nitro-1H-pyrrole-2-carboxamide hydrochloride

m.p. 178-181 °C

PMR (DMSO-d_6) δ: 10.24 (s, 1H), 8.42 (t, J=5.8 Hz, 1H), 8.18 (s, 1H), 7.72 (m, 1H), 7.67 (m, 1H), 7.65 (m, 2H), 7.28 (d, J=1.7 Hz, 1H), 6.92 (d, J=1.7 Hz, 1H), 3.95 (s, 3H), 3.85 (s, 3H), 3.66 (m, 2H), 3.39 (m, 2H), 2.73 (m, 6H);

1-methyl-N-(1-methyl-5-{[(2-{[(methylamino)(methylimino)methyl]amino}propyl)amino]carbonyl}-1H-pyrrol-3-yl)-4-nitro-1H-pyrrole-2-carboxamide hydrochloride;

1-methyl-N-(1-methyl-5-{[(2-{[(methylamino)(methylimino)methyl]amino}ethyl)amino]carbonyl}-1H-pyrrol-3-yl)-4-{[(1-methyl-4-nitro-1H-pyrrol-2-yl)carbonyl]amino}-1H-pyrrole-2-carboxamide hydrochloride

m.p. 211-214 °C

PMR (DMSO-d_6) δ: 10.15 (s, 1H), 9.99 (s, 1H), 8.31 (t, J=5.8 Hz, 1H), 8.18 (s, 1H), 7.72 (m, 2H), 7.57 (m, 1H), 7.26 (d, J=1.7 Hz, 1H), 7.23 (d, J=1.7 Hz, 1H), 7.11 (d, J=1.7 Hz, 1H), 7.05 (d, J=1.7 Hz, 1H), 6.92 (d, J=1.7 Hz, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 3.54 (m, 2H), 3.39 (m, 2H), 2.76 (m, 6H);

1-methyl-N-(1-methyl-5-{[(2-{[(methylamino)(methylimino)

methyl]amino}propyl)amino]carbonyl}-1H-pyrrol-3-yl)-4-{[(1-methyl-4-nitro-1H-pyrrol-2-yl)carbonyl]amino}-1H-pyrrole-2-carboxamide hydrochloride;

N-(2-{[amino(hydroxyimino)methyl]amino}ethyl)-1-methyl-4-nitro-1H-pyrrole-2-carboxamide;

N-(5-{[(2-{[amino(hydroxyimino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-1-methyl-4-nitro-1H-pyrrole-2-carboxamide;

N-(5-{[(2-{[amino(hydroxyimino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-1-methyl-4-{[(1-methyl-4-nitro-1H-pyrrol-2-yl)carbonyl]amino}-1H-pyrrole-2-carboxamide;

N-[2-(1H-imidazol-2-ylamino)ethyl]-1-methyl-4-nitro-1H-pyrrole-2-carboxamide hydrochloride;

N-[5-({[2-(1H-imidazol-2-ylamino)ethyl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]-1-methyl-4-nitro-1H-pyrrole-2-carboxamide hydrochloride;

N-[5-({[2-(1H-imidazol-2-ylamino)ethyl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]-1-methyl-4-{[(1-methyl-4-nitro-1H-pyrrol-2-yl)carbonyl]amino}-1H-pyrrole-2-carboxamide hydrochloride;

1-methyl-4-nitro-N-[2-(1,4,5,6-tetrahydro-2-pyrimidinylamino)ethyl]-1H-pyrrole-2-carboxamide hydrochloride;

1-methyl-N-[1-methyl-5-({[2-(1,4,5,6-tetrahydro-2-pyrimidinylamino)ethyl]amino}carbonyl)-1H-pyrrol-3-yl]-4-nitro-1H-pyrrole-2-carboxamide hydrochloride;

1-methyl-4-{[(1-methyl-4-nitro-1H-pyrrol-2-yl)carbonyl]amino}-N-[1-methyl-5-({[2-(1,4,5,6-tetrahydro-2-pyrimidinylamino)ethyl]amino}carbonyl)-1H-pyrrol-3-yl]-1H-pyrrole-2-carboxamide hydrochloride;

1-methyl-4-nitro-N-[2-(1,4,5,6-tetrahydro-2-pyrimidinylamino)propyl]-1H-pyrrole-2-carboxamide hydrochloride;

1-methyl-N-[1-methyl-5-({[2-(1,4,5,6-tetrahydro-2-pyrimidinylamino)propyl]amino}carbonyl)-1H-pyrrol-3-yl]-4-nitro-1H-pyrrole-2-carboxamide hydrochloride;

1-methyl-4-{[(1-methyl-4-nitro-1H-pyrrol-2-yl)carbonyl]amino}-N-[1-methyl-5-({[2-(1,4,5,6-tetrahydro-2-pyrimidinylamino)propyl]amino}carbonyl)-1H-pyrrol-3-yl]-1H-pyrrole-2-carboxamide hydrochloride;

Step II: The intermediate N-[2-(4,5-dihydro-1H-imidazol-2-ylamino)ethyl]-1-methyl-4-amino-1H-pyrrole-2-carboxamide dihydrochloride

1.25 g of intermediate (Step I) was dissolved in methanol (100 ml), treated with 1N hydrochloric acid solution (2 ml) and reduced over Pd catalyst (10% on charcoal) under hydrogen atmosphere (60 psi) into a Parr apparatus. The solution obtained after filtration of the catalyst was evaporated in vacuum and the solid residue washed with dry ethanol to yield 750 mg of the intermediate as a brown powder.

PMR (DMSO-d_6) δ: 10.05 (bs, 3H), 8.68 (bs, 2H), 8.46 (t, J=5.8 Hz, 1H), 8.37 (t, J=5.8 Hz, 1H), 8.14 (d, J=1.7 Hz, 1H), 7.54 (d, J=1.7 Hz, 1H), 3.89 (s, 3H), 3.46 (m, 4H), 3.50 (m, 2H), 3.35 (m, 2H).

By analogous procedure and by using the opportune starting materials the following compounds can be obtained:

N-[2-(4,5-dihydro-1H-imidazol-2-ylamino)propyl]-1-methyl-4-amino-1H-pyrrole-2-carboxamide dihydrochloride;

N-(2-{[amino(imino)methyl]amino}propyl)-1-methyl-4-amino-1H-pyrrole-2-carboxamide dihydrochloride

PMR (DMSO-d_6) δ: 10.33 (bs, 3H), 8.02 (t, J=5.8 Hz, 1H), 7.83 (m, 1H), 7.56 (m, 1H), 7.49 (bs, 4H), 7.22 (m, 1H), 3.77 (s, 3H), 3.36(m, 4H), 1.37 (m, 2H);

N-[2-(4,5-dihydro-1H-imidazol-2-ylamino)butyl]-1-methyl-4-amino-1H-pyrrole-2-carboxamide dihydrochloride;

N-[5-({[2-(4,5-dihydro-1H-imidazol-2-ylamino)ethyl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]-1-methyl-4-amino-1H-pyrrole-2-carboxamide dihydrochloride

PMR (DMSO-d_6) δ: 10.36 (bs, 3H), 10.25 (s, 1H), 8.49 (m, 2H), 8.41 (t, J=5.8 Hz, 1H), 8.23 (t, J=5.8 Hz, 1H), 8.17

(d, J=1.7 Hz, 1H), 7.61 (d, J=1.7 Hz, 1H), 7.26 (d, J=1.7 Hz, 1H), 6.90 (d, J=1.7 Hz, 1H), 4.14 (m, 2H), 3.95 (s, 3H), 3.81 (s, 3H), 3.50(m, 2H), 3.52 (m, 4H);

N-[5-({[2-(4,5-dihydro-1H-imidazol-2-ylamino)propyl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]-1-methyl-4-amino-1H-pyrrole-2-carboxamide dihydrochloride;

N-(2-{[amino(imino)methyl]amino}ethyl)-1-methyl-4-{[(1-methyl-4-amino-1H-pyrrol-2-yl)carbonyl]amino}-1H-pyrrole-2-carboxamide dihydrochloride

PMR (DMSO-d_6) δ: 10.38 (bs, 3H), 10.30 (s, 1H), 8.21 (t, J=5.8 Hz, 1H), 7.69 (m, 1H), 7.68 (m, 1H), 7.55 (m, 1H), 7.20 (m, 1H), 7.14 (bs, 4H), 6.85 (m, 1H), 3.91 (s, 3H), 3.81 (s, 3H), 3.03(m, 4H), 1.45 (m, 2H);

N-[5-({[2-(4,5-dihydro-1H-imidazol-2-ylamino)ethyl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]-1-methyl-4-{[(1-methyl-4-amino-1H-pyrrol-2-yl)carbonyl]amino}-1H-pyrrole-2-carboxamide dihydrochloride

PMR (DMSO-d_6) δ: 10.35 (bs, 3H), 10.32 (s, 1H), 10.02 (s, 1H), 8.37 (m, 2H), 8.33 (t, J=5.8 Hz, 1H), 8.20 (t, J=5.8 Hz, 1H), 8.17 (m, 1H), 7.65 (d, J=1.7 Hz, 1H), 7.28 (d, J=1.7 Hz, 1H), 7.21 (m, 1H), 7.06 (d, J=1.7 Hz, 1H), 6.94 (d, J=1.7 Hz, 1H), 3.97 (m, 2H), 3.95 (s, 3H), 3.91 (s, 3H), 3.87 (s, 3H), 3.45 (m, 2H), 3.52 (m, 4H);

N-[5-({[2-(4,5-dihydro-1H-imidazol-2-ylamino)propyl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]-1-methyl-4-{[(1-methyl-4-amino-1H-pyrrol-2-yl)carbonyl]amino}-1H-pyrrole-2-carboxamide dihydrochloride;

N-(5-{[(2-{[amino(imino)methyl]amino}propyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-1-methyl-4-{[(1-methyl-4-amino-1H-pyrrol-2-yl)carbonyl]amino}-1H-pyrrole-2-carboxamide dihydrochloride

PMR (DMSO-d_6) δ: 10.20 (bs, 3H), 10.15 (s, 1H), 9.90 (s, 1H), 8.21 (t, J=5.8 Hz, 1H), 8.11 (m, 1H), 7.26 (m, 1H), 7.24 (bs, 4H), 7.22 (m, 1H), 7.11 (m, 1H), 7.08 (m, 1H), 7.05 (m, 2H), 6.99 (m, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 3.81 (s, 3H), 3.36(m, 4H), 1.18 (m, 2H);

N-(5-{[(2-{[amino(imino)methyl]amino}butyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-1-methyl-4-{[(1-methyl-4-amino-1H-pyrrol-2-yl)carbonyl]amino}-1H-pyrrole-2-carboxamide dihydrochloride;

N-(2-{[amino(methylimino)methyl]amino}ethyl)-1-methyl-4-amino-1H-pyrrole-2-carboxamide dihydrochloride;

N-(5-{[(2-{[amino(methylimino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-1-methyl-4-amino-1H-pyrrole-2-carboxamide dihydrochloride;

N-(5-{[(2-{[amino(methylimino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-1-methyl-4-{[(1-methyl-4-amino-1H-pyrrol-2-yl)carbonyl]amino}-1H-pyrrole-2-carboxamide dihydrochloride;

N-(2-{[imino(methylamino)methyl]amino}ethyl)-1-methyl-4-amino-1H-pyrrole-2-carboxamide dihydrochloride;

N-(5-{[(2-{[imino(methylamino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-1-methyl-4-amino-1H-pyrrole-2-carboxamide dihydrochloride;

N-(5-{[(2-{[imino(methylamino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-1-methyl-4-{[(1-methyl-4-amino-1H-pyrrol-2-yl)carbonyl]amino}-1H-pyrrole-2-carboxamide dihydrochloride;

N-(2-{[(dimethylamino)(imino)methyl]amino}ethyl)-1-methyl-4-amino-1H-pyrrole-2-carboxamide dihydrochloride;

N-(5-{[(2-{[(dimethylamino)(imino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-1-methyl-4-amino-1H-pyrrole-2-carboxamide dihydrochloride;

N-(5-{[(2-{[(dimethylamino)(imino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-1-methyl-4-{[(1-methyl-4-amino-1H-pyrrol-2-yl)carbonyl]amino}-1H-pyrrole-2-carboxamide dihydrochloride;

1-methyl-N-(2-{[(methylamino)(methylimino)methyl]amino}ethyl)-4-amino-1H-pyrrole-2-carboxamide dihydrochloride

PMR (DMSO-d_6) δ: 10.03 (bs, 3H), 8.87 (t, J=5.8 Hz, 1H), 7.75 (m, 2H), 7.66 (s, 1H), 7.56 (m, 1H), 7.53 (s, 1H), 3.85 (s, 3H), 3.28 (m, 4H), 2.66 (m, 6H);

1-methyl-N-(2-{[(methylamino)(methylimino)methyl]amino}

propyl)-4-amino-1H-pyrrole-2-carboxamide dihydrochloride;
1-methyl-N-(1-methyl-5-{[(2-{[(methylamino)(methylimino)methyl]amino}ethyl)amino]carbonyl}-1H-pyrrol-3-yl)-4-amino-1H-pyrrole-2-carboxamide dihydrochloride

PMR (DMSO-d_6) δ: 10.23 (bs, 3H), 10.17 (s, 1H), 8.36 (t, J=5.8 Hz, 1H), 7.82 (m, 1H), 7.72 (m, 1H), 7.68 (m, 1H), 7.54 (m, 2H), 7.22 (m, 1H), 6.94 (m, 1H), 3.97 (s, 3H), 3.78 (s, 3H), 3.44 (m, 2H), 3.27 (m, 2H), 2.58(m, 6H);
1-methyl-N-(1-methyl-5-{[(2-{[(methylamino)(methylimino)methyl]amino}propyl)amino]carbonyl}-1H-pyrrol-3-yl)-4-amino-1H-pyrrole-2-carboxamide dihydrochloride;
1-methyl-N-(1-methyl-5-{[(2-{[(methylamino)(methylimino)methyl]amino}ethyl)amino]carbonyl}-1H-pyrrol-3-yl)-4-{[(1-methyl-4-amino-1H-pyrrol-2-yl)carbonyl]amino}-1H-pyrrole-2-carboxamide dihydrochloride

PMR (DMSO-d_6) δ: 10.22 (s, 1H), 10.15 (s, 1H), 10.01 (s, 1H), 8.28 (t, J=5.8 Hz, 1H), 7.78 (m, 2H), 7.57 (m, 1H), 7.46 (m, 1H), 7.26 (m, 1H), 7.21 (m, 1H), 7.02 (m, 1H), 6.96 (m, 1H), 6.81 (m, 1H), 3.81 (s, 3H), 3.74 (s, 3H), 3.65 (s, 3H), 3.38 (m, 2H), 3.26 (m, 2H), 2.64 (m, 6H);
1-methyl-N-(1-methyl-5-{[(2-{[(methylamino)(methylimino)methyl]amino}propyl)amino]carbonyl}-1H-pyrrol-3-yl)-4-{[(1-methyl-4-amino-1H-pyrrol-2-yl)carbonyl]amino}-1H-pyrrole-2-carboxamide dihydrochloride;
N-(2-{[amino(hydroxyimino)methyl]amino}ethyl)-1-methyl-4-amino-1H-pyrrole-2-carboxamide hydrochloride;
N-(5-{[(2-{[amino(hydroxyimino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-1-methyl-4-amino-1H-pyrrole-2-carboxamide hydrochloride;
N-(5-{[(2-{[amino(hydroxyimino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-1-methyl-4-{[(1-methyl-4-amino-1H-pyrrol-2-yl)carbonyl]amino}-1H-pyrrole-2-carboxamide hydrochloride;
N-[2-(1H-imidazol-2-ylamino)ethyl]-1-methyl-4-amino-1H-pyrrole-2-carboxamide dihydrochloride;
N-[5-({[2-(1H-imidazol-2-ylamino)ethyl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]-1-methyl-4-amino-1H-pyrrole-2-

carboxamide dihydrochloride;
N-[5-({[2-(1H-imidazol-2-ylamino)ethyl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]-1-methyl-4-{[(1-methyl-4-amino-1H-pyrrol-2-yl)carbonyl]amino}-1H-pyrrole-2-carboxamide dihydrochloride;
1-methyl-4-amino-N-[2-(1,4,5,6-tetrahydro-2-pyrimidinylamino)ethyl]-1H-pyrrole-2-carboxamide dihydrochloride;
1-methyl-N-[1-methyl-5-({[2-(1,4,5,6-tetrahydro-2-pyrimidinylamino)ethyl]amino}carbonyl)-1H-pyrrol-3-yl]-4-amino-1H-pyrrole-2-carboxamide dihydrochloride;
1-methyl-4-{[(1-methyl-4-amino-1H-pyrrol-2-yl)carbonyl]amino}-N-[1-methyl-5-({[2-(1,4,5,6-tetrahydro-2-pyrimidinylamino)ethyl]amino}carbonyl)-1H-pyrrol-3-yl]-1H-pyrrole-2-carboxamide dihydrochloride;
1-methyl-4-amino-N-[2-(1,4,5,6-tetrahydro-2-pyrimidinylamino)propyl]-1H-pyrrole-2-carboxamide dihydrochloride;
1-methyl-N-[1-methyl-5-({[2-(1,4,5,6-tetrahydro-2-pyrimidinylamino)propyl]amino}carbonyl)-1H-pyrrol-3-yl]-4-amino-1H-pyrrole-2-carboxamide dihydrochloride;
1-methyl-4-{[(1-methyl-4-amino-1H-pyrrol-2-yl)carbonyl]amino}-N-[1-methyl-5-({[2-(1,4,5,6-tetrahydro-2-pyrimidinylamino)propyl]amino}carbonyl)-1H-pyrrol-3-yl]-1H-pyrrole-2-carboxamide dihydrochloride.

Step III The title compound

A solution of 4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carbonyl chloride (175 mg), prepared as reported in WO 97/43258, in dioxane (40 ml), was added dropwise at room temperature to a solution of the intermediate obtained from step II (205 mg) and $NaHCO_3$ (150 mg) in a mixture water/dioxane 2/1 (60 ml). The solution was stirred for 2 hours, the solvent was evaporated in vacuum and the crude residue was purified by flash chromatography (methylene chloride/methanol:8/2) to give the title compound (175 mg; y = 60%)as a white solid.

FAB-MS: m/z 749(100, $[M+H]^+$)

PMR (DMSO-d_6) δ: 10.30 (s, 1H), 9.95 (s, 1H), 9.92 (s, 1H), 9.90 (s, 1H), 8.24(m, 1H), 8.06 (bt, 1H), 7.23 (d, J=1.6 Hz, 1H), 7.22 (d, J=1.6 Hz, 1H), 7.21 (d, J=1.6 Hz, 1H) 7.16 (d, J=1.6 Hz, 1H), 7.06 (d, J=1.6 Hz, 1H), 7.05 (d, J=1.6 Hz, 1H), 7.03 (d, J=1.6 Hz, 1H), 6.95 (d, J=1.6 Hz, 1H), 6.68 (d, J=3.0 Hz, 1H), 6.21 (d, J=3.0 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.80 (s, 3H), 3.77 (s, 3H), 3.58 (s, 4H), 3.40-3.20 (m, 4H).

By analogous procedure and by using the opportune starting materials the following compounds can be obtained:

N-(5-{[(5-{[(5-{[(2-{[amino(methylimino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride **(comp.1)**;

N-(5-{[(5-{[(5-{[(2-{[amino(methylimino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-chloroacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride **(comp.2)**;

4-[(2-bromoacryloyl)amino]-N-(5-{[(5-{[(5-{[(2-{[imino(methylamino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-1-methyl-1H-pyrrole-2-carboxamide hydrochloride **(comp.3)**;

4-[(2-chloroacryloyl)amino]-N-(5-{[(5-{[(5-{[(2-{[imino(methylamino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-1-methyl-1H-pyrrole-2-carboxamide hydrochloride **(comp.4)**;

4-[(2-bromoacryloyl)amino]-N-(5-{[(5-{[(5-{[(2-{[(dimethylamino)(imino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-1-methyl-1H-pyrrole-2-carboxamide hydrochloride **(comp.5)**;

4-[(2-chloroacryloyl)amino]-N-(5-{[(5-{[(5-{[(2-{[(dimethylamino)(imino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-1-methyl-1H-pyrrole-2-carboxamide hydrochloride **(comp.6)**;

4-[(2-bromoacryloyl)amino]-1-methyl-N-(1-methyl-5-{[(1-methyl-5-{[(1-methyl-5-{[(2-{[(methylamino)(methylimino)methyl]amino}ethyl)amino]carbonyl}-1H-pyrrol-3-yl)amino]carbonyl}-1H-pyrrol-3-yl)amino]carbonyl}-1H-pyrrol-3-yl)-1H-pyrrole-2-carboxamide hydrochloride **(comp.7)**

FAB-MS: m/z 751(100, $[M+H]^+$)

PMR (DMSO-d_6) δ: 10.28 (s, 1H), 9.94 (s, 1H), 9.91 (s, 1H), 9.90 (s, 1H), 8.16(bt, 1H), 7.52(bq, 2H), 7.43(bt, 1H), 7.22 (d, J=1.6 Hz, 1H), 7.21 (d, J=1.6 Hz, 1H), 7.20 (d, J=1.6 Hz, 1H) 7.18 (d, J=1.6 Hz, 1H), 7.06 (d, J=1.6 Hz, 1H), 7.05 (d, J=1.6 Hz, 1H), 7.03 (d, J=1.6 Hz, 1H), 6.93 (d, J=1.6 Hz, 1H), 6.67 (d, J=3.0 Hz, 1H), 6.21 (d, J=3.0 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 3.40-3.20 (m, 4H), 2.73 (d, J=4.5Hz 6H);

4-[(2-chloroacryloyl)amino]-1-methyl-N-(1-methyl-5-{[(1-methyl-5-{[(1-methyl-5-{[(2-{[(methylamino)(methylimino)methyl]amino}ethyl)amino]carbonyl}-1H-pyrrol-3-yl)amino]carbonyl}-1H-pyrrol-3-yl)amino]carbonyl}-1H-pyrrol-3-yl)-1H-pyrrole-2-carboxamide hydrochloride **(comp.8)**;

N-(5-{[(5-{[(5-{[(2-{[amino(hydroxyimino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide **(comp.13)**;

N-(5-{[(5-{[(5-{[(2-{[amino(hydroxyimino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-chloroacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide **(comp.14)**;

4-[(2-chloroacryloyl)amino]-N-[5-({[5-({[5-({[2-(4,5-dihydro-1H-imidazol-2-ylamino)ethyl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride **(comp.16)**;

4-[(2-bromoacryloyl)amino]-N-[5-({[5-({[5-({[2-(1H-imidazol-2-ylamino)ethyl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride **(comp. 17)**;

4-[(2-chlorooacryloyl)amino]-N-[5-({[5-({[5-({[2-(1H-imidazol-2-ylamino)ethyl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride **(comp.18)**;

4-[(2-bromoacryloyl)amino]-1-methyl-N-[1-methyl-5-({[1-methyl-5-({[1-methyl-5-({[2-(1,4,5,6-tetrahydro-2-pyrimidinylamino)ethyl]amino}carbonyl)-1H-pyrrol-3-yl]amino}carbonyl)-1H-pyrrol-3-yl]amino}carbonyl)-1H-pyrrol-3-yl]-1H-pyrrole-2-carboxamide hydrochloride **(comp.19)**;

4-[(2-chloroacryloyl)amino]-1-methyl-N-[1-methyl-5-({[1-methyl-5-({[1-methyl-5-({[2-(1,4,5,6-tetrahydro-2-pyrimidinylamino)ethyl]amino}carbonyl)-1H-pyrrol-3-yl]amino}carbonyl)-1H-pyrrol-3-yl]amino}carbonyl)-1H-pyrrol-3-yl]-1H-pyrrole-2-carboxamide hydrochloride **(comp.20)**;

N-(5-{[(5-{[(5-{[(2{[amino(imino)methyl]amino}propyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride **(comp.21)**

FAB-MS: m/z 749(100, $[M+H]^+$)

PMR (DMSO-d_6) δ: 10.30 (s, 1H), 9.95 (s, 1H), 9.92 (s, 1H), 9.90 (s, 1H), 8.24(m, 1H), 8.06 (bt, 1H), 7.23 (d, J=1.6 Hz, 1H), 7.22 (d, J=1.6 Hz, 1H), 7.21 (d, J=1.6 Hz, 1H)

7.16 (d, J=1.6 Hz, 1H), 7.06 (d, J=1.6 Hz, 1H), 7.05 (d, J=1.6 Hz, 1H), 7.03 (d, J=1.6 Hz, 1H), 6.95 (d, J=1.6 Hz, 1H), 6.68 (d, J=3.0 Hz, 1H), 6.21 (d, J=3.0 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.80 (s, 3H), 3.77 (s, 3H), 3.58 (s, 4H), 3.40-3.20 (m, 4H);

N-(5-{[(5-{[(5-{[(2{[amino(imino)methyl]amino}propyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-chloroacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride **(comp.22)**;

4-[(2-bromoacryloyl)amino]-1-methyl-N-(1-methyl-5-{[(1-methyl-5-{[(1-methyl-5-{[(2-{[(methylamino)(methylimino)methyl]amino}propyl)amino]carbonyl}-1H-pyrrol-3-yl)amino]carbonyl}-1H-pyrrol-3-yl)amino]carbonyl}-1H-pyrrol-3-yl)-1H-pyrrole-2-carboxamide hydrochloride **(comp.23)**;

4-[(2-chloroacryloyl)amino]-1-methyl-N-(1-methyl-5-{[(1-methyl-5-{[(1-methyl-5-{[(2-{[(methylamino)(methylimino)methyl]amino}propyl)amino]carbonyl}-1H-pyrrol-3-yl)amino]carbonyl}-1H-pyrrol-3-yl)amino]carbonyl}-1H-pyrrol-3-yl)-1H-pyrrole-2-carboxamide hydrochloride **(comp.24)**;

4-[(2-bromoacryloyl)amino]-N-[5-({[5-({[5-({[2-(4,5-dihydro-1H-imidazol-2-ylamino)propyl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride **(comp.27)**;

4-[(2-chloroacryloyl)amino]-N-[5-({[5-({[5-({[2-(4,5-dihydro-1H-imidazol-2-ylamino)propyl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride **(comp.28)**;

4-[(2-bromoacryloyl)amino]-1-methyl-N-[1-methyl-5-({[1-methyl-5-({[1-methyl-5-({[2-(1,4,5,6-tetrahydro-2-pyrimidinylamino)propyl]amino}carbonyl)-1H-pyrrol-3-yl]amino}carbonyl)-1H-pyrrol-3-yl]amino}carbonyl)-1H-

pyrrol-3-yl]-1H-pyrrole-2-carboxamide hydrochloride **(comp.29)**;

4-[(2-chloroacryloyl)amino]-1-methyl-N-[1-methyl-5-({[1-methyl-5-({[1-methyl-5-({[2-(1,4,5,6-tetrahydro-2-pyrimidinylamino)propyl]amino}carbonyl)-1H-pyrrol-3-yl]amino}carbonyl)-1H-pyrrol-3-yl]amino}carbonyl)-1H-pyrrol-3-yl]-1H-pyrrole-2-carboxamide hydrochloride **(comp.30)**;

N-(5-{[(5-{[(2-{[amino(methylimino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride **(comp.31)**;

4-[(2-bromoacryloyl)amino]-1-methyl-N-(1-methyl-5-{[(1-methyl-5-{[(2-{[(methylamino)(methylimino)methyl]amino}ethyl)amino]carbonyl}-1H-pyrrol-3-yl)amino]carbonyl}-1H-pyrrol-3-yl)-1H-pyrrole-2-carboxamide hydrochloride **(comp.32)**;

4-[(2-bromoacryloyl)amino]-1-methyl-N-(1-methyl-5-{[(1-methyl-5-{[(2-[(aminocarbonyl)amino]ethyl)amino]carbonyl}-1H-pyrrol-3-yl)amino]carbonyl}-1H-pyrrol-3-yl)-1H-pyrrole-2-carboxamide hydrochloride **(comp.33)**;

4-[(2-bromoacryloyl)amino]-N-[5-({[5-({[2-(4,5-dihydro-1H-imidazol-2-ylamino)ethyl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride **(comp.34)**;

4-[(2-bromoacryloyl)amino]-1-methyl-N-[1-methyl-5-({[1-methyl-5-({[1-methyl-5-({[2-(1,4,5,6-tetrahydro-2-pyrimidinylamino)ethyl]amino}carbonyl)-1H-pyrrol-3-yl]amino}carbonyl)-1H-pyrrol-3-yl]amino}carbonyl)-1H-pyrrol-3-yl]-1H-pyrrole-2-carboxamide hydrochloride **(comp.35)**;

N-(5-{[(5-{[(5-{[(2{[amino(imino)methyl]amino}butyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-

1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide **(comp.36)**

FAB-MS: m/z 752(80, $[M+H]^+$)

PMR (DMSO-d6) d: 10.25 (s, 1H), 9.96 (s, 1H), 9.95 (s, 1H), 9.92 (s, 1H), 8.06 (bt, 1H), 7.22 (d, J=1.6 Hz, 1H), 7.21 (d, J=1.6 Hz, 1H), 7.20 (d, J=1.6 Hz, 1H) 7.18 (d, J=1.6 Hz, 1H), 7.07 (d, J=1.6 Hz, 1H), 7.06 (d, J=1.6 Hz, 1H), 7.03 (d, J=1.6 Hz, 1H), 6.93 (d, J=1.6 Hz, 1H), 6.68 (d, J=3.0 Hz, 1H), 6.21 (d, J=3.0 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.80 (s, 3H), 3.77 (s, 3H), 3.58 (s, 4H), 3.19-3.21 (m, 2H);3.12-3.18 (m, 2H);1.42-1.50 (m, 4H);

N-(5-{[(5-{[(5-{[(2{[amino(imino)methyl]amino}butyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-chloroacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide **(comp.37)**.

Example 3

N-{5-[({5-[({5-[({2-[(aminocarbonyl)amino]ethyl}amino)carbonyl]-1-methyl-1H-pyrrol-3-yl}amino)carbonyl]-1-methyl-1H-pyrrol-3-yl}amino)carbonyl]-1-methyl-1H-pyrrol-3-yl}-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide **(comp.9)**

Step I: The intermediate tert-butyl 2-{[(1-methyl-4-nitro-1H-pyrrol-2-yl)carbonyl]amino}ethylcarbamate

To a solution of tert-butyl 2-aminoethylcarbamate (1.6 g) and triethylamine (1.5 ml) in dry dioxane (20 ml), a solution of 1-methyl-4-nitro-1H-pyrrole-2-carbonyl chloride (2 g) in dry dioxane (10 ml) was added dropwise at room temperature. The reaction was stirred for 3h, the solvent allowed under vacuum and the crude residue purified by flash chromatography (methylene chloride/methanol:8/2) giving the intermediate (2.63 g, y= 81%) as a white powder.

m.p. 178-180 °C

PMR (DMSO-d_6) δ: 8.38 (t, J=7.4 Hz, 1H), 8.12 (m, 1H), 7.39

(m, 1H), 6.90 (t, J=7.4 Hz, 1H), 3.89 (s, 3H), 3.23 (m, 2H), 3.07 (m, 2H), 1.36 (s, 9H).

By analogous procedure and by using the opportune starting materials the following compounds can be obtained:

tert-butyl 2-{[(1-methyl-4-{[(1-methyl-4-nitro-1H-pyrrol-2-yl)carbonyl]amino}-1H-pyrrol-2-yl)carbonyl]amino} ethylcarbamate

m.p. 211-214 °C

PMR (DMSO-d_6) δ: 10.24 (s, 1H), 8.18 (m, 1H), 8.03 (m, 1H), 7.59 (d, J=1.7HZ, 1H), 7.21 (d, J=1.7HZ, 1H), 6.86 (m, 2H), 3.95 (s, 3H), 3.81 (s, 3H), 3.19 (m, 2H), 3.06 (m, 2H), 1.38 (s, 9H);

tert-butyl 2-{[(1-methyl-4-{[(1-methyl-4-nitro-1H-pyrrol-2-yl)carbonyl]amino}-1H-pyrrol-2-yl)carbonyl]amino} propylcarbamate;

tert-butyl 2-{[(1-methyl-4-{[(1-methyl-4-{[(1-methyl-4-nitro-1H-pyrrol-2-yl)carbonyl]amino}-1H-pyrrol-2-yl)carbonyl]amino}-1H-pyrrol-2-yl)carbonyl]amino}ethylcarbamate

m.p. 256-258 °C

PMR (DMSO-d_6) δ: 10.30 (s, 1H), 9.96 (s, 1H), 8.19 (m, 1H), 7.99 (m, 1H), 7.59 (m, 1H), 7.28 (d, J=1.7HZ, 1H), 7.20 (d, J=1.7HZ, 1H), 7.03 (d, J=1.7HZ, 1H), 6.87 (m, 2H), 3.96 (s, 3H), 3.90 (s, 3H), 3.80 (s, 3H), 3.22 (m, 2H), 3.04 (t, J=5.6Hz,2H), 1.38 (s, 9H);

tert-butyl 2-{[(1-methyl-4-{[(1-methyl-4-{[(1-methyl-4-nitro-1H-pyrrol-2-yl)carbonyl]amino}-1H-pyrrol-2-yl)carbonyl]amino}-1H-pyrrol-2-yl)carbonyl]amino}propylcarbamate;

Step II: The intermediate tert-butyl 2-{[(1-methyl-4-amino-1H-pyrrol-2-yl)carbonyl]amino}ethylcarbamate

To a suspension of 10% Pd/C (100 mg) in a mixture of MeOH/H_2O 1/1 (20 ml) at 0 °C, NaBH4 (684 mg) and intermediate of step *I* (1.87 g) were added and stirred for 1h.

The catalyst was removed by filtration and the solvent allowed under vacuum. The residue dissolved in EtOAc (15 ml), washed with water (20 ml) then brine (40 ml) and finally dried over Na_2SO_4 anhydrous.

The solvent was allowed under vacuum yielding the intermediate (1.44 g, y = 85%) as a yellow oil which is used without further purification in the next step.

By analogous procedure and by using the opportune starting materials the following compounds can be obtained:

tert-butyl 2-{[(1-methyl-4-amino-1H-pyrrol-2-yl)carbonyl]amino}propylcarbamate;

tert-butyl 2-{[(1-methyl-4-{[(1-methyl-4-amino-1H-pyrrol-2-yl)carbonyl]amino}-1H-pyrrol-2-yl)carbonyl]amino} ethylcarbamate;

tert-butyl 2-{[(1-methyl-4-{[(1-methyl-4-amino-1H-pyrrol-2-yl)carbonyl]amino}-1H-pyrrol-2-yl)carbonyl]amino} propylcarbamate;

tert-butyl 2-{[(1-methyl-4-{[(1-methyl-4-{[(1-methyl-4-amino-1H-pyrrol-2-yl)carbonyl]amino}-1H-pyrrol-2-yl) carbonyl]amino}-1H-pyrrol-2-yl)carbonyl]amino}ethylcarbamate;

tert-butyl 2-{[(1-methyl-4-{[(1-methyl-4-{[(1-methyl-4-amino-1H-pyrrol-2-yl)carbonyl]amino}-1H-pyrrol-2-yl) carbonyl]amino}-1H-pyrrol-2-yl)carbonyl]amino}propylcarbamate;

N-{5-[({2-[(aminocarbonyl)amino]ethyl}amino)carbonyl]-1-methyl-1H-pyrrol-3-yl}-1-methyl-4-{[(1-methyl-4-amino-1H-pyrrol-2-yl)carbonyl]amino}-1H-pyrrole-2-carboxamide.

Step III: The intermediate N-{5-[({2-[(aminocarbonyl)amino]ethyl}amino)carbonyl]-1-methyl-1H-pyrrol-3-yl}-1-methyl-4-{[(1-methyl-4-nitro-1H-pyrrol-2-yl)carbonyl]amino}-1H-pyrrole-2-carboxamide

A solution of the intermediate tert-butyl 2-{[(1-methyl-4-{[(1-methyl-4-{[(1-methyl-4-nitro-1H-pyrrol-2-yl)carbonyl]amino}-1H-pyrrol-2-yl)carbonyl]amino}-1H-

pyrrol-2-yl)carbonyl]amino}ethylcarbamate (270 mg), in 5N HCl/methanol (20 ml) was stirred at room temperature for 2 h. The solvent was allowed under vacuum and the residue dissolved in DMF (5 ml). To the DMF solution was cooled at 0 °C TEA (70 ml) and CDI (100 mg) were added. The reaction was stirred a room temperature for 3 h, the solvent allowed under vacuum, the solid residue dissolved in EtOAc (20 ml), and washed with H_2O (20 ml). The separated organic phase was dried over Na_2SO_4 anhydrous, the solvent evaporated in vacuum and the solid residue dissolved in EtOH. The alcoholic solution was cooled at 0 °C and saturated with ammonia gas. The reaction solution was stirred for 3 h at room temperature, the solvent removed under vacuum and the crude residue purified by flash chromatography (DCM/MeOH:8/2) to give the intermediate (200 mg, y = 80%) as a yellow solid.

m.p. 256-258 °C

PMR (DMSO-d_6) δ: 10.30 (s, 1H), 9.97 (s, 1H), 8.62 (m, 1H), 8.23(s, 1H), 8.19 (m, 1H), 7.66 (d, J=1.7 Hz, 1H), 7.59 (m, 1H), 7.25 (d, J=1.7 Hz, 1H), 7.21 (d, J=1.7 Hz, 1H), 7.07 (s, 2H), 6.87 (d, J=1.7 Hz, 1H), 3.96 (s, 3H), 3.86 (s, 3H), 3.80 (s, 3H), 3.35 (m, 4H).

By analogous procedure and by using the opportune starting materials the following compounds can be obtained:

N-{5-[({2-[(aminocarbonyl)amino]propyl}amino)carbonyl]-1-methyl-1H-pyrrol-3-yl}-1-methyl-4-{[(1-methyl-4-nitro-1H-pyrrol-2-yl)carbonyl]amino}-1H-pyrrole-2-carboxamide;

N-{5-[({2-{[(methylamino)carbonyl]amino}ethylyl}amino)carbonyl]-1-methyl-1H-pyrrol-3-yl}-1-methyl-4-{[(1-methyl-4-nitro-1H-pyrrol-2-yl)carbonyl]amino}-1H-pyrrole-2-carboxamide;

N-{5-[({2-{[(methylamino)carbonyl]amino}propyl}amino)carbonyl]-1-methyl-1H-pyrrol-3-yl}-1-methyl-4-{[(1-methyl-4-nitro-1H-pyrrol-2-yl)carbonyl]amino}-1H-pyrrole-2-carboxamide.

Step IV: The title compound

To a solution of the intermediate N-{5-[({2-[(aminocarbonyl)amino]ethyl}amino)carbonyl]-1-methyl-1H-pyrrol-3-yl}-1-methyl-4-{[(1-methyl-4-amino-1H-pyrrol-2-yl)carbonyl]amino}-1H-pyrrole-2-carboxamide (350 mg), $NaHCO_3$ (412 mg) in a mixture water/dioxane 2/1 (80 ml) a solution of 4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carbonyl chloride prepared as reported in WO97/43258 (287 mg) in dioxane (50 ml) was added dropwise at room temperature. The solution was stirred for 2 hours, the solvent was evaporated in vacuum and the crude residue was purified by flash chromatography (DCM/MeOH:8/2) to give the title compound (435 mg; y = 60%)as a yellow powder.
FAB-MS: m/z 725(80, $[M+H]^+$)
PMR (DMSO-d_6) δ: 10.32 (s, 1H), 9.96 (s, 1H), 9.94 (s, 1H), 9.92 (s, 1H), 8.60 (m, 1H), 8.21(s, 1H), 8.17 (m, 2H), 7.66 (d, J=1.7 Hz, 1H), 7.59 (m, 2H), 7.25 (d, J=1.7 Hz, 1H), 7.22 (m, 1H), 7.05 (s, 2H), 6.87 (d, J=1.7 Hz, 1H), 6.67 (d, J=3.0 Hz, 1H), 6.21 (d, J=3.0 Hz, 1H), 3.94 (s, 3H), 3.85 (s, 3H), 3.82 (s, 3H), 3.80 (s, 3H), 3.35 (m, 4H).
By analogous procedure and by using the opportune starting materials the following compounds can be obtained:
N-{5-[({5-[({5-[({2-[(aminocarbonyl)amino]ethyl}amino)carbonyl]-1-methyl-1H-pyrrol-3-yl}amino)carbonyl]-1-methyl-1H-pyrrol-3-yl}amino)carbonyl]-1-methyl-1H-pyrrol-3-yl}-4-[(2-chloroacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide **(comp.10)**;

4-[(2-bromoacryloyl)amino]-1-methyl-N-(1-methyl-5-{[(1-methyl-5-{[(1-methyl-5-{[(2-{[(methylamino)carbonyl]amino}ethyl)amino]carbonyl}-1H-pyrrol-3-yl)amino]carbonyl}-1H-pyrrol-3-yl)amino]carbonyl}-1H-pyrrol-3-yl)-1H-pyrrole-2-carboxamide **(comp.11)**;

4-[(2-chloroacryloyl)amino]-1-methyl-N-(1-methyl-5-{[(1-methyl-5-{[(1-methyl-5-{[(2-{[(methylamino)carbonyl]amino}ethyl)amino]carbonyl}-1H-pyrrol-3-yl)amino]carbonyl}-1H-pyrrol-3-yl)amino]carbonyl}-1H-pyrrol-3-yl)-1H-pyrrole-2-carboxamide **(comp.12)**.

Example 4

Tablets each weighing 0.250 g and containing 50 mg of the active substance can be manufactured as follows:

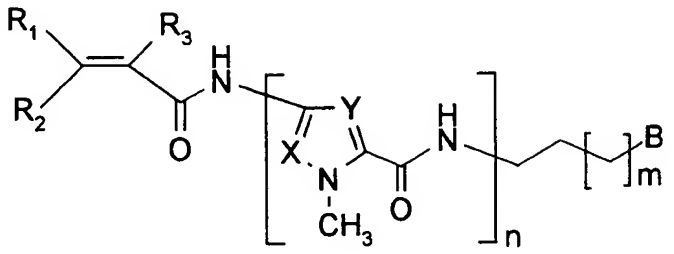
Composition for 10,000 tablets	
N-(5-{[(5-{[(5-{[(2{[amino(imino)methyl]Amino}propyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride (comp.21)	500 g
Lactose	1,400 g
Corn starch	500 g
Talc powder	80 g
Magnesium stearate	20 g

N-(5-{[(5-{[(5-{[(2{[amino(imino)methyl]amino}propyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride, lactose and half of the corn starch were mixed; the mixture was then forced through a sieve of 0.5 mm mesh size.

Corn starch (10 g) was suspended in warm water (90 ml) and the resulting paste was used to granulate the powder. The granulate was dried, comminuted on a sieve of 1.4 mm mesh size, then the remaining quantity of starch, talc and magnesium stearate was added, carefully mixed and processed into tablets.

CLAIMS

1. A compound which is an acryloyl peptidic derivative of formula



(I)

wherein:

n is 3 or 4;

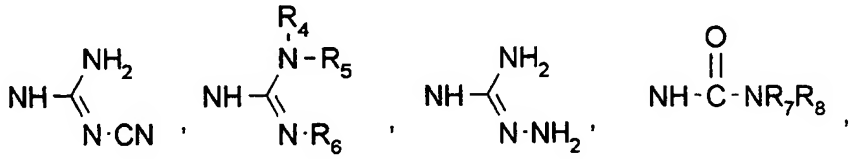
m is 0, 1 or 2;

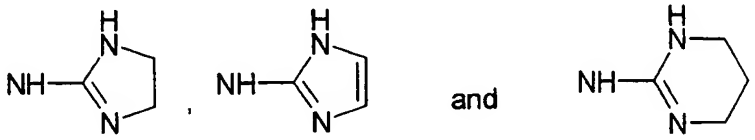
X and Y are the same or different and are selected, independently for each heterocyclic ring, from N or CH;

R_1 and R_2, the same or different, are selected from hydrogen, halogen or C_1-C_4 alkyl;

R_3 is hydrogen or halogen;

B is selected from the groups consisting of:





wherein R_4, R_5, R_7 and R_8 are, independently from each other, hydrogen or C_1-C_4 alkyl; R_6 is hydrogen, hydroxy or C_1-C_4 alkyl; or a pharmaceutically acceptable salt thereof;

provided that:

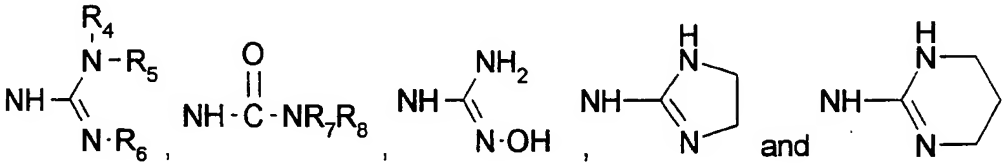
i) X and Y are not both N atoms for the same heterocyclic ring;

ii) when all of X and Y are CH groups and m is 0, then at least one of R_4, R_5 or R_6 is other than hydrogen;

iii) when at least one of X and Y is other than CH, then at least one of R_4 and R_5 is other than hydrogen.

2. A compound of formula (I) according to claim 1 wherein R_4, R_5, R_7 and R_8 are, independently from each other, hydrogen, methyl or ethyl and R_6 is hydrogen, hydroxy, methyl or ethyl.

3. A compound of formula (I) according to claim 1 wherein
n is 3 or 4;
m is 0, 1 or 2;
X and Y are CH;
R_1 and R_2 are hydrogen;
R_3 is chlorine or bromine;
B is selected from



wherein R_4, R_5, R_7 and R_8 are, independently from each other, hydrogen or methyl and R_6 is hydrogen, hydroxy or methyl; provided that when m is 0, at least one of R_4, R_5 or R_6 is other than hydrogen.

4. A compound of formula (I) according to claim 1, and the pharmaceutically acceptable salts, selected from the group consisting of:

(1) N-(5-{[(5-{[(5-{[(2-{[amino(methylimino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide

(2) N-(5-{[(5-{[(5-{[(2-{[amino(methylimino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-chloroacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide

(3) 4-[(2-bromoacryloyl)amino]-N-(5-{[(5-{[(5-{[(2-{[imino(methylamino)methyl]amino}ethyl)amino]carbonyl}

-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-1-methyl-1H-pyrrole-2-carboxamide

(4) 4-[(2-chloroacryloyl)amino]-N-(5-{[(5-{[(5-{[(2-{[imino(methylamino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-1-methyl-1H-pyrrole-2-carboxamide

(5) 4-[(2-bromoacryloyl)amino]-N-(5-{[(5-{[(5-{[(2-{[(dimethylamino)(imino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-1-methyl-1H-pyrrole-2-carboxamide

(6) 4-[(2-chloroacryloyl)amino]-N-(5-{[(5-{[(5-{[(2-{[(dimethylamino)(imino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-1-methyl-1H-pyrrole-2-carboxamide

(7) 4-[(2-bromoacryloyl)amino]-1-methyl-N-(1-methyl-5-{[(1-methyl-5-{[(1-methyl-5-{[(2-{[(methylamino)(methylimino)methyl]amino}ethyl)amino]carbonyl}-1H-pyrrol-3-yl)amino]carbonyl}-1H-pyrrol-3-yl)amino]carbonyl}-1H-pyrrol-3-yl)-1H-pyrrole-2-carboxamide

(8) 4-[(2-chloroacryloyl)amino]-1-methyl-N-(1-methyl-5-{[(1-methyl-5-{[(1-methyl-5-{[(2-{[(methylamino)(methylimino)methyl]amino}ethyl)amino]carbonyl}-1H-pyrrol-3-yl)amino]carbonyl}-1H-pyrrol-3-yl)amino]carbonyl}-1H-pyrrol-3-yl)-1H-pyrrole-2-carboxamide

(9) N-{5-[({5-[({5-[({2-[(aminocarbonyl)amino]ethyl}amino)carbonyl]-1-methyl-1H-pyrrol-3-yl}amino)carbonyl]-1-methyl-1H-pyrrol-3-yl}amino)carbonyl]-1-methyl-1H-pyrrol-3-yl}-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide

(10) N-{5-[({5-[({5-[({2-[(aminocarbonyl)amino]ethyl}amino)carbonyl]-1-methyl-1H-pyrrol-3-yl}amino)carbonyl]-1-methyl-1H-pyrrol-3-yl}amino)carbonyl]-1-methyl-1H-pyrrol-3-yl}-4-[(2-

chloroacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide

(11) 4-[(2-bromoacryloyl)amino]-1-methyl-N-(1-methyl-5-{[(1-methyl-5-{[(1-methyl-5-{[(2-{[(methylamino)carbonyl]amino}ethyl)amino]carbonyl}-1H-pyrrol-3-yl)amino]carbonyl}-1H-pyrrol-3-yl)amino]carbonyl}-1H-pyrrol-3-yl)-1H-pyrrole-2-carboxamide

(12) 4-[(2-chloroacryloyl)amino]-1-methyl-N-(1-methyl-5-{[(1-methyl-5-{[(1-methyl-5-{[(2-{[(methylamino)carbonyl]amino}ethyl)amino]carbonyl}-1H-pyrrol-3-yl)amino]carbonyl}-1H-pyrrol-3-yl)amino]carbonyl}-1H-pyrrol-3-yl)-1H-pyrrole-2-carboxamide

(13) N-(5-{[(5-{[(5-{[(2-{[amino(hydroxyimino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide

(14) N-(5-{[(5-{[(5-{[(2-{[amino(hydroxyimino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-chloroacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide

(15) 4-[(2-bromoacryloyl)amino]-N-[5-({[5-({[5-({[2-(4,5-dihydro-1H-imidazol-2-ylamino)ethyl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]-1-methyl-1H-pyrrole-2-carboxamide

(16) 4-[(2-chloroacryloyl)amino]-N-[5-({[5-({[5-({[2-(4,5-dihydro-1H-imidazol-2-ylamino)ethyl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]-1-methyl-1H-pyrrole-2-carboxamide

(17) 4-[(2-bromoacryloyl)amino]-N-[5-({[5-({[5-({[2-(1H-imidazol-2-ylamino)ethyl]amino}carbonyl)-1-methyl-1H-

pyrrol-3-yl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]-1-methyl-1H-pyrrole-2-carboxamide

(18) 4-[(2-chlorooacryloyl)amino]-N-[5-({[5-({[5-({[2-(1H-imidazol-2-ylamino)ethyl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]-1-methyl-1H-pyrrole-2-carboxamide

(19) 4-[(2-bromoacryloyl)amino]-1-methyl-N-[1-methyl-5-({[1-methyl-5-({[1-methyl-5-({[2-(1,4,5,6-tetrahydro-2-pyrimidinylamino)ethyl]amino}carbonyl)-1H-pyrrol-3-yl]amino}carbonyl)-1H-pyrrol-3-yl]amino}carbonyl)-1H-pyrrol-3-yl]-1H-pyrrole-2-carboxamide

(20) 4-[(2-chloroacryloyl)amino]-1-methyl-N-[1-methyl-5-({[1-methyl-5-({[1-methyl-5-({[2-(1,4,5,6-tetrahydro-2-pyrimidinylamino)ethyl]amino}carbonyl)-1H-pyrrol-3-yl]amino}carbonyl)-1H-pyrrol-3-yl]amino}carbonyl)-1H-pyrrol-3-yl]-1H-pyrrole-2-carboxamide

(21) N-(5-{[(5-{[(5-{[(2{[amino(imino)methyl]amino}propyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide

(22) N-(5-{[(5-{[(5-{[(2{[amino(imino)methyl]amino}propyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-chloroacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide

(23) 4-[(2-bromoacryloyl)amino]-1-methyl-N-(1-methyl-5-{[(1-methyl-5-{[(1-methyl-5-{[(2-{[(methylamino)(methylimino)methyl]amino}propyl)amino]carbonyl}-1H-pyrrol-3-yl)amino]carbonyl}-1H-pyrrol-3-yl)amino]carbonyl}-1H-pyrrol-3-yl)-1H-pyrrole-2-carboxamide

(24) 4-[(2-chloroacryloyl)amino]-1-methyl-N-(1-methyl-5-{[(1-methyl-5-{[(1-methyl-5-{[(2-{[(methylamino)(methylimino)methyl]amino}propyl)amino]carbonyl}-1H-

pyrrol-3-yl)amino]carbonyl}-1H-pyrrol-3-yl)amino]carbonyl}-1H-pyrrol-3-yl)-1H-pyrrole-2-carboxamide

(25) N-{5-[({5-[({5-[({2-[(aminocarbonyl)amino]ethyl}amino)carbonyl]-1-methyl-1H-pyrrol-3-yl}amino)carbonyl]-1-methyl-1H-pyrrol-3-yl}amino)carbonyl]-1-methyl-1H-pyrrol-3-yl}-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide

(26) N-{5-[({5-[({5-[({2-[(aminocarbonyl)amino]ethyl}amino)carbonyl]-1-methyl-1H-pyrrol-3-yl}amino)carbonyl]-1-methyl-1H-pyrrol-3-yl}amino)carbonyl]-1-methyl-1H-pyrrol-3-yl}-4-[(2-chloroacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide

(27) 4-[(2-bromoacryloyl)amino]-N-[5-({[5-({[5-({[2-(4,5-dihydro-1H-imidazol-2-ylamino)propyl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]-1-methyl-1H-pyrrole-2-carboxamide

(28) 4-[(2-chloroacryloyl)amino]-N-[5-({[5-({[5-({[2-(4,5-dihydro-1H-imidazol-2-ylamino)propyl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]-1-methyl-1H-pyrrole-2-carboxamide

(29) 4-[(2-bromoacryloyl)amino]-1-methyl-N-[1-methyl-5-({[1-methyl-5-({[1-methyl-5-({[2-(1,4,5,6-tetrahydro-2-pyrimidinylamino)propyl]amino}carbonyl)-1H-pyrrol-3-yl]amino}carbonyl)-1H-pyrrol-3-yl]amino}carbonyl)-1H-pyrrol-3-yl]-1H-pyrrole-2-carboxamide

(30) 4-[(2-chloroacryloyl)amino]-1-methyl-N-[1-methyl-5-({[1-methyl-5-({[1-methyl-5-({[2-(1,4,5,6-tetrahydro-2-pyrimidinylamino)propyl]amino}carbonyl)-1H-pyrrol-3-yl]amino}carbonyl)-1H-pyrrol-3-yl]amino}carbonyl)-1H-pyrrol-3-yl]-1H-pyrrole-2-carboxamide

(31) N-(5-{[(5-{[(2-{[amino(methylimino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide

(32) 4-[(2-bromoacryloyl)amino]-1-methyl-N-(1-methyl-5-{[(1-methyl-5-{[(2-{[(methylamino)(methylimino)methyl]amino}ethyl)amino]carbonyl}-1H-pyrrol-3-yl)amino]carbonyl}-1H-pyrrol-3-yl)-1H-pyrrole-2-carboxamide

(33) 4-[(2-bromoacryloyl)amino]-1-methyl-N-(1-methyl-5-{[(1-methyl-5-{[(2-[(aminocarbonyl)amino]ethyl)amino]carbonyl}-1H-pyrrol-3-yl)amino]carbonyl}-1H-pyrrol-3-yl)-1H-pyrrole-2-carboxamide

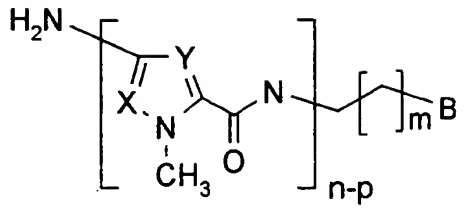
(34) 4-[(2-bromoacryloyl)amino]-N-[5-({[5-({[2-(4,5-dihydro-1H-imidazol-2-ylamino)ethyl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]-1-methyl-1H-pyrrole-2-carboxamide

(35) 4-[(2-bromoacryloyl)amino]-1-methyl-N-[1-methyl-5-({[1-methyl-5-({[1-methyl-5-({[2-(1,4,5,6-tetrahydro-2-pyrimidinylamino)ethyl]amino}carbonyl)-1H-pyrrol-3-yl]amino}carbonyl)-1H-pyrrol-3-yl]amino}carbonyl)-1H-pyrrol-3-yl]-1H-pyrrole-2-carboxamide

(36) N-(5-{[(5-{[(5-{[(2{[amino(imino)methyl]amino}butyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide

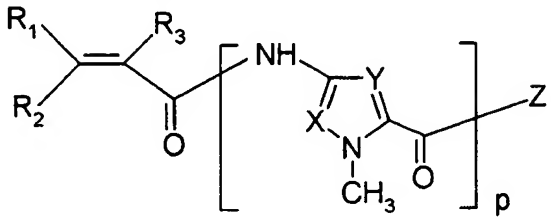
(37) N-(5-{[(5-{[(5-{[(2{[amino(imino)methyl]amino}butyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-chloroacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide.

5. A process for preparing a compound of formula (I), as defined in claim 1, which comprises reacting a compound of formula



(II)

with a compound of formula



(III)

wherein n, m, X, Y, B, R_1, R_2, R_3, X and Y are as defined above; p is 0 or 1 and Z is hydroxy or a suitable leaving group; and, if desired, converting a compound of formula (I) into a pharmaceutically acceptable salt thereof.

6. A process according to claim 5 wherein Z is hydroxy or a leaving group selected from chlorine, 2,4,5-trichlorophenoxy or pivaloyl.

7. A compound of formula (I) as defined in any one of claims from 1 to 3 for use in a method of treating the human or animal body by therapy.

8. A compound of formula (I) according to claim 7 for use as an antineoplastic agent.

9. Use of a compound of formula (I) as defined in any one of claims from 1 to 3 in the manufacture of a medicament for use in the treatment of cancer.

10. A pharmaceutical composition which comprises an effective amount of a compound of formula (I) as defined in any one of claims from 1 to 3 as an active principle, in association with one or more pharmaceutically acceptable carriers and/or diluents.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 00/11714

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D207/34 C07D403/14 A61P35/02 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	WO 96 05196 A (PHARMACIA SPA :BERIA ITALO (IT); PESENTI ENRICO (IT); CAPOLONGO LA) 22 February 1996 (1996-02-22) cited in the application the whole document	1-10
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 April 2001	12/04/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040. Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scruton-Evans, I

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INTERNATIONAL SEARCH REPORT

Intern .nal Application No
PCT/EP 00/11714

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	H.H.LEE: "Pyrazole analogues of the bispyrrolecarboxamide antitumour antibiotics" ANTICANCER DRUG DESIGN, vol. 6, 1991, pages 501-517, XP000994914 cited in the application the whole document	1-10
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INTERNATIONAL SEARCH REPORT

Information on patent family members

Interr. nal Application No
PCT/EP 00/11714

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